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Emerging pathways driving early synaptic pathology in Alzheimer's disease

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ABSTRACT

The current state of the AD research field is highly dynamic is some respects, while seemingly stagnant in others. Regarding the former, our current lack of understanding of initiating disease mechanisms, the absence of effective treatment options, and the looming escalation of AD patients is energizing new research directions including a much-needed re-focusing on early pathogenic mechanisms, validating novel targets, and investigating relevant biomarkers, among other exciting new efforts to curb disease progression and foremost, preserve memory function. With regard to the latter, the recent disappointing series of failed Phase III clinical trials targeting Aβ and APP processing, in concert with poor association between brain Aβ levels and cognitive function, have led many to call for a re-evaluation of the primacy of the amyloid cascade hypothesis. In this review, we integrate new insights into one of the earliest described signaling abnormalities in AD pathogenesis, namely intracellular Ca^{2+} signaling disruptions, and focus on its role in driving synaptic deficits – which is the feature that does correlate with AD-associated memory loss. Excess Ca^{2+}release from intracellular stores such as the endoplasmic reticulum (ER) has been well-described in cellular and animal models of AD, as well as human patients, and here we expand upon recent developments in ER-localized release channels such as the IP_3R and RyR, and the recent emphasis on RyR2. Consistent with ER Ca^{2+} mishandling in AD are recent findings implicating aspects of SOCE, such as STIM2 function, and TRPC3 and TRPC6 levels. Other Ca^{2+}-regulated organelles important in signaling and protein handling are brought into the discussion, with new perspectives on lysosomal regulation. These early signaling abnormalities are discussed in the context of synaptic pathophysiology and disruptions in synaptic plasticity with a particular emphasis on short-term plasticity deficits. Overall, we aim to update and expand the list of early neuronal signaling abnormalities implicated in AD pathogenesis, identify specific channels and organelles involved, and link these to proximal synaptic impairments driving the memory loss in AD. This is all within the broader goal of identifying novel therapeutic targets to preserve cognitive function in AD.

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Abbreviations

Aβ	amyloid β
AHP	after-hyperpolarization
AMPA-R	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid sensitive glutamate receptor
ApoE	apolipoprotein E
APP	amyloid precursor protein
CICR	Ca^{2+} induced Ca^{2+} release
ER	endoplasmic reticulum
GPCR	G-protein coupled receptor
I_{CRAC}	Ca^{2+} release activated Ca^{2+} current
IP3	inositol trisphosphate
IP3R	inositol trisphosphate receptor
LMO4	Lim only domain protein 4
LTD	long-term depression
LTP	long-term potentiation
MAM	mitochondria-associated membrane
mGluR	metabotropic glutamate receptor
NMDA-R	N-methyl-D-aspartate sensitive glutamate receptor
PPF	paired-pulse facilitation
PTP	post-tetanic potentiation
RyR	ryanodine receptor
SK	small-conductance Ca^{2+} activated K^+ channel
SERCA	sarco/endoplasmic reticulum Ca^{2+} ATPase
SOCE	store-operated Ca^{2+} entry
TREM	triggering receptor expressed on myeloid cells
VGCC	voltage-gated Ca^{2+} channel

1. Urgency in AD

Among the devastating neurodegenerative diseases, Alzheimer's disease (AD) alone afflicts over 5 million individuals in the U.S., and is feared to grow to nearly 14 million by 2050. Available FDA-approved therapeutics are limited to three cholinesterase inhibitors, approved in 1996–2000, and a low affinity NMDA-R antagonist, approved in 2003. These are symptomatic treatments, not cures, and are not effective in all patients. While the amyloid hypothesis still largely predominates in the field, decades of research and clinic trials addressing Aβ production and deposition have yet to provide a mechanistic cause of AD or offer new therapeutics. Although expectations and efforts remain high for targeting APP processing as the keystone for AD [136], the amyloid cascade hypothesis is being met with increasing skepticism and scrutiny [20,21,59]. While ongoing clinical trials take a view more towards preventing than reversing AD, clearly it also is time to increase efforts in earlier or upstream mechanisms that may cause or contribute to AD.

As recognized since 1989, it is synapse loss which correlates best with cognitive impairment [36,55,128,150]. This association makes intuitive sense and provides a direct cause for the cognitive impairment in AD, as intact synaptic structure and function are required for the synaptic encoding that forms stable memories [56,96]. By extension, it stands to reason that preserving synapses would be an effective means to prevent loss of cognitive functions in at-risk populations. Until recently, there were few tools to measure synaptic integrity in the human brain prior to autopsy, and studies linking synaptic function to cognitive resilience were largely conducted in mouse models or from post mortem human tissue samples [4,24,41]. However, the recent identification of a PET ligand to measure synaptic density in human patients [44] is an exciting new tool, and stands to provide meaningful diagnostic and predictive information related to synapse loss in disease progression.

Most AD patients, over 95%, have sporadic or late-onset forms of the disease where the etiology is unknown, although ApoE4 is a well-characterized genetic risk factor [34,42,99] and more recently variants in TREM2, which normally serves to trigger phagocytosis, have been identified [102]. In familial AD (FAD), the disease-causing mutations identified to date are in *presenilin-1* and *2* (PS1 and PS2) and in *amyloid precursor protein (APP)* genes. Although APP and PS mutations lead to increased Aβ production or changes in Aβ42:40 ratios [136], Aβ-directed potential therapeutics so far have not met efficacy milestones with regards to memory function in human patients, while multiple lines of evidence connect PS mutations identified in early-onset AD with neuronal dysfunction and apoptosis through Ca^{2+} dyshomeostasis [37,40]. While Aβ is an obligate diagnostic criterion for AD, it is critically important to expand research in other risk factor mechanisms among cells in the CNS [25,35].

2. Fundamental and early role of ER Ca^{2+} dysregulation in AD-related synaptic deficits

Ca^{2+} is well known as a principal factor in cytotoxicity and apoptosis, and Ca^{2+} dyshomeostasis is seen in neurons with aging, AD and AD transgenic animal models [17,46,143]. Indeed, PS1 mutations alone, as would occur in FAD, impact Ca^{2+} signaling at early or asymptomatic disease stages in the absence of Aβ or tau aggregation [25,37,120,122,141,148]. The initiation of this early pathogenic cascade may be due to the γ-secretase *in*dependent association of PS with inositol trisphosphate receptors (IP_3R) and ryanodine receptors (RyR), the two major Ca^{2+} release channels in the endoplasmic reticulum. FAD-linked mutant PS can directly increase the gating properties of IP_3R and increase the intracellular Ca^{2+} signaling response to IP_3-generating GPCR ligands [100,139]. This is seen in cell models, in brain slice pyramidal neurons from multiple AD mouse models, and, importantly, in ectodermal cells (fibroblasts) taken directly from human AD patients [80,139,144]. Both PS1 and PS2 influence RyR2 gating through direct interaction with the PS cytosolic domain, with PS1 increasing channel open probability and single channel currents at physiological Ca^{2+} concentrations ($\leq$1 μM) [131] and PS2 reducing feedback inhibition of RyR2 by Ca^{2+} at pathological concentrations ($\geq$10 μM) [58,115]. In aged mice, PS1 expression is reduced in cerebellum and PS2 levels are increased in cerebellum and forebrain, potentially contributing to age-related increases in cytosolic Ca^{2+} and cytotoxic elevation of Ca^{2+} through other mechanisms [69].

RyRs are the other major Ca^{2+} release channel in the ER. While both RyR and IP_3R activities are potentiated by Ca^{2+}, it is RyR that is largely responsible for Ca^{2+}-induced Ca^{2+} release (CICR) in neurons as well as skeletal muscle, cardiac muscle and other cells [25,37,133]. As such, RyR are poised to amplify other signals elevating cytoplasmic Ca^{2+}. Indeed, Aβ has been found to increase Ca^{2+} in AD cell and animal models [38,111,153] and elevated Ca^{2+} can increase Aβ production [37,66,118,125,142] resulting in a pathogenic feed-forward cycle. RyR-mediated Ca^{2+} release is markedly up-regulated in single AD transgenic mice expressing mutant PS, in AD transgenics expressing a combination of gene mutations, and in APP mutant mice [25,37]. RyR-evoked Ca^{2+} responses are increased in soma cytoplasm 2–3 fold and up to an order of magnitude in dendrite and spines in the presence or absence of Aβ deposits and from youth throughout life in the

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